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Electron microscopy of SARS-CoV-2: a challenging task

Authors' reply

We thank Cynthia Goldsmith and colleagues for their interest in our recent Correspondence.¹ We described autopsy findings from patients who had died from COVID-19 and showed a systemic endotheliitis with evidence of loss of integrity of the endothelial monolayer.¹

The framework of endotheliitis provides an explanation for the unique predilection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in those individuals with hypertension, diabetes, or established cardiovascular disease, a group known to have pre-existing endothelial dysfunction. COVID-19-endotheliitis could also explain impaired microcirculatory function across different organs and the frequently observed prothrombotic state with in-situ clot formation. Endothelial infection and injury by SARS-CoV-1 has been shown.² Our demonstration of viral particles using electron microscopy (EM) is supported by several reports independently describing ultrastructural round virus-like particles in the setting of a SARS-CoV-2 infection.^{3–6} We demonstrated tubulo-reticular structures in the immediate vicinity of the spherical particles that are strikingly identical to SARS-CoV-1-associated membrane changes described by Goldsmith and colleagues in 2004.⁷ In our EM thin-section images, the virus-like particles were relatively large (mean diameter 180 nm [SD 10]). However, subsequent analysis of more EM images has revealed a mean particle size of 67 nm (SD 15 nm, median 65 nm, 95% CI 41–102; n=33). Zhu and colleagues⁵ noted that SARS-CoV-2 virions ranged from “about 60 to 140 nm”. In another recent study,⁶ virus-like particles in patients with confirmed SARS-CoV-2 infection were 70–110 nm in diameter. By comparison, SARS-CoV-1 viral particles analysed

with the same technique (ultrathin EM imaging) were 50–80 nm in diameter.^{7–10}

Goldsmith and colleagues have studied coronavirus isolates grown in cell culture, whereas our EM data of virus-like particles were obtained from a post-mortem kidney allograft obtained during autopsy. Since most other recent reports of patients with COVID-19 also describe post-mortem findings, it remains unclear to what extent tissue type (cell culture, fresh biopsy material, or autopsy material), time to fixation, and post-mortem autolysis alter subcellular structures in preparation for EM. This notwithstanding, these observed particles in patients with COVID-19 should be best designated as virus-like particles because definitive assignment of these structures as SARS-CoV-2 virions requires immuno-EM.

Investigations with vascular organoids that preceded our observations¹ showed that SARS-CoV-2 can infect human blood vessels via the ACE2 pathways, providing the first and direct evidence that the virus can indeed invade human vasculature.¹¹ Our findings have also been confirmed in descriptions of renal tropism of SARS-CoV-2, with detection of SARS-CoV-2 protein in human glomerular endothelial and epithelial cells.¹²

Importantly, our demonstration of virus cell infection in the kidney and endotheliitis¹ points to a general host inflammatory response causing hyperinflammation as a principal participant in the vascular pathology of COVID-19. Endothelial cell dysfunction, which might subsequently induce a prothrombotic state, could thus explain the vascular microcirculatory complications seen in different organs in patients with COVID-19.

We declare no competing interests.

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